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EXAMINER	
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DATE MAILED: 08/05/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 4/21/97 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-15 are pending in the application.
   Of the above, claims 4 & 9-14 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☐ Claims 1-3, 5-8, & 15 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

Part III DETAILED ACTION

1. Claims 1-15 are pending. Claims 1-3, 5-8, and 15 are currently under examination.

Claim Rejections - 35 USC § 112

2. The enablement rejection of claims 1-3, 5-8, and 15 under 35 U.S.C. 112, first paragraph is withdrawn.

New grounds for rejection:

3. The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed. The specification is objected to with regards to the subject matter of claims 1-3, 5-8, and 15 pertaining to "in an amount sufficient to induce production of antibodies to said second antigen in said patient". The specification, as originally filed, does not explicitly or implicitly teach a method of treatment comprising administering bispecific antibodies to induce production of antibodies to a targeted antigen.

4. Claims 1-3, 5-8, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of targeted cell lysis, does not reasonably provide enablement for a method of treating tumors by inducing production of antibodies to a target antigen in a patient. The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. Claims 1-3, and 6-8 are drawn to a method of inducing an immune response in a patient comprising using a bispecific antibody wherein the first binding site recognizes FcγRIII and a second binding site recognizes c-erbB-2 and wherein the bispecific antibody induces production of antibodies to the tumor antigen. The specification fails to enable one of skill in the art how to treat tumors by inducing the production of antibodies. The specification teaches using the bispecific antibody to induce targeted cytolysis. The specification does not teach that induction of antibodies are useful for treating tumors. It is well known in the art that anti-tumor antibodies are present in cancer patients. It is also well known in the art that the antibodies are ineffective in treating the tumor due to immune suppression. The specification does not teach how treat a tumor by inducing the production of antibodies. The specification only teaches treating tumors by targeted cytolysis. Targeted cytolysis would not be expected to eliminate or reduce immune suppression. This is demonstrated by the very nature of the treatment method which involves stimulating individual cytolytic cells to kill tumor cells by being tethered via the bispecific antibody.

Claim Rejections - 35 USC § 103

6. Claims 1-3, 5-8, and 15 remain rejected under 35 U.S.C. § 103 as being unpatentable over Hsieh-Ma et al. (Cancer Research 1992) or Weiner et al. (Cancer Research 1993) or Ring et al. (Breast Epithelial Antigens 1991) in view of Fanger et al. (Critical Reviews in Immunology 1992).

The claims are drawn to a method of inducing an immune response in a patient, comprising a bispecific antibody wherein the first binding site recognizes FcγRIII and a second binding site recognizes the cancer antigen c-erbB-2. The claims are further limited to wherein the bispecific antibody is 2B1 (CRL 10197).

Hsieh-Ma et al. teach using 2B1 to induce an immune response in the form of targeted cytolysis. Hsieh-Ma et al. teach that 2B1 could mediate lysis of tumor cells expressing c-erbB-2 in the presence of all blood components found *in vitro* (p.6834 column 2 and 6835 column 1). Hsieh-Ma et al. also teach that 2B1 as an interesting candidate for possible clinical evaluation in patients with c-erbB-2 positive carcinomas (p. 6838). Hsieh-Ma et al. does not teach inducing an immune response in patients with 2B1.

Weiner et al. teach using 2B1 to induce an immune response in the form of targeted cytolysis. Weiner et al. teach that 2B1 was effective in inhibiting the growth of human tumor cell line

xenografts expressing c-erbB-2 in mice (p.97). Weiner et al. does not teach inducing an immune response in patients with 2B1.

Ring et al. (Breast Epithelial Antigens 1991) teach using 2B1 to induce an immune response in the form of promoting the lysis of tumor cells expressing c-erbB-2 by human large granular lymphocytes and macrophages *in vitro* (p.91). Ring et al. state: "we look forward to future evaluation of 2B1...in animal models and human clinical trials. Ring et al. does not teach using 2B1 to induce an immune response in patients.

Fanger et al. teach a review of using bispecific antibodies to induce an immune response in the form of targeted cytolysis in human patients. Fanger et al. teach using bispecific antibodies in targeted cytolysis wherein one the binding sites binds FcγRIII. The references cited within Fanger et al. teach the methods of administrating bispecific antibodies as well as, doses, duration of treatment, etc.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the bispecific antibody 2B1 as taught by Hsieh-Ma et al., Weiner et al. and Ring et al. to induce an immune response in patients in the form of target cytolysis as taught by Fanger et al. One of ordinary skill in the art at the time the invention was made would have been motivated to use 2B1 in patients because Hsieh-Ma et al., Weiner et al. and Ring et al. teach that 2B1 is effective in the targeted cytolysis of tumor cells, and Fanger et

al. teach bispecific antibody mediated targeted cytolysis is a promising form of cancer treatment.

7. The Examiner would like to thank Applicant for pointing out the typographical error in listing the rejected claims. Claim 5 is included in the rejection which corresponds with the restriction requirement as pointed out by Applicant. It is noted, however, that claim 9 remains withdrawn as being drawn to a non-elected specie.

The Applicant argues that the amendment to claim 1 overcomes the rejection by adding the further limitation of inducing antibodies to the tumor antigen which is not taught by the above references. Applicant's arguments have been fully considered but they are not persuasive. The claimed method appears to use the same doses as that which is routinely used in the art for treating tumors with bispecific antibodies (see Fanger). The doses that would by used in view of the above references would be the same as that claimed. Therefore, the claimed method and that of the above references would be identical. Moreover, the Applicant has not demonstrated that the induction of antibodies by the patient provides any criticality to the claim. As stated above, it is well know in the art that antibodies are produced by cancer patients to their tumor cells yet the antibodies are ineffective killing the tumor cells.

8. No Claims are allowable.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John M. Lucas whose telephone number is (703) 305-6838. The examiner can normally be reached on T-F from 7:00am to 6:00pm EST.

11. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax phone number for this Group is (703) 305-3014 or 305-7939.

12. Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [lila.feisee@uspto.gov].

13. All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

14. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John M. Lucas, PhD

1 August 1997

Toni R. Scheiner

TONI R. SCHEINER
PRIMARY EXAMINER
GROUP 1800